REMARKS

Claims 22-24 and 28 are currently pending.

Applicants thank the Examiner for withdrawing the previous objection to the specification.

CLAIM REJECTIONS

Rejection of claims under 35 U.S.C. § 103(a)

Collins and Van Der Mei

I.Collins and Van Der Mei Do Not Provide Motivation for a Person of Skill in the Art to Use Bifidobacterium sp. 420 in the Method of Collins

The Examiner has maintained the rejection of claims 22-24 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Publication No. 2002/0006432 to Collins ("Collins") in view of Van Der Mei, *J. Med. Microbiol.,* Vol. 49, p. 713-718 (2000) ("Van Der Mei"). See Office Action at p. 4. Claims 23-24 depend from independent claim 22.

Independent claim 22 relates to a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-l mRNA in at least one epithelial cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

The Examiner states that "Collins teaches a method of treating a subject by administering bacteria of the genus *Bifidobacterium* to a subject (abstract)." See Office Action at p. 4. While the Examiner acknowledges that Collins "does not specifically teach the use of *Bifidobacterium* sp. 420 in the method of using the bacteria," the Examiner alleges that "[o]ne of ordinary skill in the art would have been motivated to use *Bifidobacterium* sp. 420 in the method of Collins because Collins teaches that **any** species of *Bifidobacterium* with probiotic effects may be used in the method, ad further teaches methods for testing such strains for probiotic effects (p. 2, par. 14-15, p. 4, par. 81-83)(emphasis added)." See Office Action at p. 4-5. Applicants respectfully traverse these statements.

MPEP 2145, paragraph X. A, states that "[a]ny judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in that art at the time the claimed invention was made and **does not include knowledge gleaned only from applicant's**

disclosure, such a reconstruction is proper" (emphasis added by Applicants) (citing In *re McLaughlin* 443 F.2d 1392, 1395 (CCPA 1971)).

When viewed as a whole, Collins relates to specific strains of *Bifidobacterium longum infantis* and, without hindsight, a person of ordinary skill in the art would not have considered the teachings of Collins to be applicable to all *Bifidobacterium* strains. For example, Collins at paragraph [0014] states that "[t]he invention provides **a** strain of Bifidobacterium isolated from resected and washed human gastrointestinal tract which is significantly immunomodulatory following oral consumption in humans." (emphasis added). Reference to the bacterium in Collins' paragraphs [0015] to [0025] is to "**the**" strain – i.e. providing antecedence back to the singular "strain" referred to in Collins' paragraph [0014]. Additionally, Collins' paragraphs [0026] to [0029] actually specify the specific strain as *Bifidobacterium longum infantis* UCC35624. All of the Figures and Examples relate to *Bifidobacterium longum infantis*. Furthermore, Collins' paragraphs [0081] to [0083] relied on by the Examiner are part of Collins' Example 1 and relate to how the *Bifidobacterium longium infantis* strains used in the later Collins' Examples were isolated. Thus, a person of ordinary skill in the art reading Collins without the benefit of impermissible hindsight afforded by the claimed invention would consider Collins to relate to *Bifidobacterium longum infantis* strains only.

Further, Collins teaches that some *Bifidobacterium* are insufficient for use in the method. Collins teaches that ascertaining the sensitivity profiles of *Bifidobacterium* to antibiotics. See Collins, paragraph [0097]. Collins further teaches that a *Bifidobacterium longum infantis* strain useful in the method needs to be resistant to acidic pH and needs to be able to survive in gastric juice; yet, Collins discloses strains that are unable to survive at acidic pH and in gastric juice. See Collins, paragraphs [0098]-[0104] and Table 2. Collins also teaches that "resistance to bile acids is an important biological strain characteristic required for survival in [the gastrointestinal tract] and in addition [the strain] must not impinge on the health of the host by producing toxic compounds such as deoxycholic [sic] (DCA) and lithocholic acid (LCA) which have been implicated in cytotoxic phenomena." See Collins, paragraph [0105]. However, some strains were unable to survive in the presence of porcine bile or cholic acid. See Collins, Tables 3 and 4. Finally, Collins teaches that different strains of *Bifidobacterium longum infantis* exhibit differing degrees of the necessary antimicrobial activity. See Collins, Tables 6 and 7.

Because Collins relates to *Bifidobacterium longum infantis* and teaches that some strains of *Bifidobacterium longum infantis* are insufficient for use in the method, Collins does not teach

that "**any** strain of *Bifidobacterium* with probiotic effects may be used in the method." Accordingly, a person of ordinary skill in the art would not have been motivated to combine Collins with any document which did not relate to a strain or strains of *Bifidobacterium longum infantis*.

The Examiner further contends that "[r]egardless of whether Van Der Mei teaches the use of the probiotic *Bifidobacterium* species taught therein for a different purpose, one of ordinary skill in the art would have recognized that a *Bifidobacterium* species could have been selected for use from a finite number of members of the species, and would further have been motivated to select the species taught in the Van Der Mei reference because it had previously been used as a probiotic." See Office Action at p. 9-10. However, as discussed above, Collins teaches that not all probiotic *Bifidobacterium* are useful in the method, and Van Der Mei does not provide any indication that *Bifidobacterium* sp. 420 has advantages over any other strain of *Bifidobacterium*, let alone that it would be advantageous in the method of Collins. To the contrary, Van Der Mei finds *Bifidobacterium* sp. 420 to be ineffective, see Abstract, which reads:

> [e]xposure of oropharyngeal biofilms on voice prostheses to suspensions of *Bifidobactrium infantis* 420 or *Enterococcus faecium* 603 did not significantly reduce the number of yeasts in the biofilm. However, suspensions of *Lactobacillus fermentum* B54, *L. rhamnosus* 744 or *L. lactis cremoris* Sk11 led to a reduction in the number of yeasts harvested from voice prostheses.

Thus, it can be seen that Van Der Mei actually teaches away from using *Bifidobactrium infantis* 420 in the method of Collins, which considers antimicrobial properties to be a factor in selecting an effective strain. Van Der Mei is silent as to whether *Bifidobacterium* sp. 420 has any of the other characteristics outlined in Collins. Van Der Mei also does not disclose positive effects of a *Bifidobacterium* strain associated with the treatment of inflammatory disease, is actually silent with regard to inflammatory disease, and does not link the specific *Bifidobacterium longum infantis* strains of Collins with other *Bifidobacterium*.

Additionally, the Examiner contends that "one of ordinary skill in the art would have recognized that a *Bifidobacterium* species could have been selected for use from a **finite** number of members of the species …" (emphasis added). See Office Action at p. 9. Applicants respectfully traverse the Examiner's conclusion. This is an improper general allegation that has no support or documentary evidence that there are finite members of *Bifidobacterium* strains. At the time of the present invention there were a huge number of *Bifidobacterium* strains available. See for example, a partial list of *Bifidobacterium* strains attached at Appendix A of Applicants'

November 1, 2010 Response. Of all of the strains available, there is nothing to motivate a person of ordinary skill in the art to select *Bifidobacterium* sp. 420 and substitute this strain in the method of Collins instead of the very specific strains of *Bifidobacterium longum infantis* taught by Collins. In view of the above, without the use of hindsight analysis, it can be seen that there is no motivation to use *Bifidobacterium* sp. 420 in the method of Collins.

Moreover, Van Der Mei discloses a completely different field of use for the bacteria component compared to their effects on cytokine secretion by peripheral blood mononuclear cells described in Collins. Van Der Mei discloses the effects of probiotic bacteria on the prevalence of yeasts in oropharyngeal biofilms on silicone rubber voice prostheses. See Van Der Mei, Abstract. There are no teachings either in Collins or in Van Der Mei which indicate that a bacteria which affects the prevalence of yeasts in oropharyngeal biofilms on silicone rubber voice prostheses would have effects on cytokine secretion by peripheral blood mononuclear cells as described in Collins. Thus, a person of ordinary skill in the art would have no motivation to combine the teachings of Collins and Van Der Mei.

In view of the above, in the absence of hindsight analysis, it can be seen that there is no motivation for a person of skill in the art to use *Bifidobacterium* sp. 420 in the method of Collins. Accordingly, Collins and Van Der Mei do not teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-l mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

Since claims 23-24 depend from independent claim 22, those claims should be patentable over the combination of Collins and Van Der Mei for at least the reasons described above. Applicants respectfully request reconsideration and the withdrawal of this rejection.

II. Unexpected Results

Applicants have argued that the claimed method provides unexpected advantages over the method of Collins. The Examiner has rejected this argument, stating "the claiming of a new use, function or unknown property that is inherently present in the prior art does not necessarily make the claim patentable (MPEP 2112)." See Office Action, p. 8. Applicants respectfully traverse this statement.

The fact that a certain result or characteristic **may occur or be present** in the prior art is **not sufficient** to establish the inherency of that result or characteristic. MPEP 2112, Paragraph

IV, citing In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is **necessarily present** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" MPEP 2112, Paragraph IV, citing In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

The Examiner asserts that "the bacterial strain (*Bifidobacterium* sp. 420) was known in the prior art, and the composition was known to be useful as a probiotic. Thus, the explanation of the mechanism by which the probiotic composition is effective does not render the claim patentable." See Office Action, p. 8.

A "probiotic" defined as "live microorganisms (including bacteria and yeasts for example) which, when for example ingested or locally applied in sufficient numbers, beneficially affects the host organism, i.e. by conferring one or more demonstrable health benefits on the host organism." See Specification, page 40, lines 15-18. Based on the definition of a probiotic, referring to *Bifidobacterium* sp. 420 as "probiotic" is not indicative of any specific use, result, characteristic or mechanism, rather it generally indicates that the bacteria provides a health benefit on the host. As further explained in the Specification,

> "Probiotics may **improve the microbial balance** in one or more mucosal surfaces. For example, the mucosal surface may be the intestine, the urinatory tract, the respiratory tract or the skin. The term "probiotic" as used herein also encompasses live microorganisms that can **stimulate the beneficial branches of the immune system** and at the same time **decrease the inflammatory reactions** in a mucosal surface, for example the gut. In this regard, the use of the composition of the present invention, containing said probiotic ingredient for **anti-cancer therapy** and **prevention of allergies and ulcerative colitis** is also contemplated."

See Specification, page 40, lines 18-26. Collins also teaches that a probiotic can act through many different pathways and achieve many different results. Collins states:

> "Furthermore, indirect evidence in humans demonstrates that consuming milk fermented by bifidobacteria can **lead to reduced levels of certain faecal enzymes** such as β-D galactosidase implicated in the **conversion of procarcinogens to carcinogens** (Bouhnik Y. et al, Eur. J. Clin. Nutr. 1996;50:269-273). Faecal-borne **putrefaction metabolities such as p-cresol, indole and ammonia were also reduced** when subjects consumed milk fermented by *Bifidobacterium longum* and *S. thermophilus* (Takiguchi, R. etal.

Bifids--Flores, Fructus et Semina 1996;9:135-140).

Antimicrobial activity has been reported to be associated with bifidobacteria. Also, bifidobacteria have been shown to **modulate various parameters of the immune system**.

Mucosal inflammation in IL-10 deficient mice has been reported to be reduced by feeding the subject animals a preparation of lactic acid bacteria (Madsen, K. et al. Gastroenterol. 1997;112:A1030.). Further studies completed in rats have demonstrated that ingestion of bifidobacteria can **suppress aberrant crypt foci (early preneoplastic lesions) formation in the colon** (Kulkarni, N. and Reddy, B. Proc. Soc. Experim. Biol. Med. 1994; 207;278-283.) in addition to significant **decreases in colon tumor incidence and in the numbers of tumors present** (Singh, J. et al Carcinogenesis 1997;18:833-841).

There is an on-going search for probiotic strains with particular beneficial effects on **nutrition and therapy and on health generally**."

See Collins, paragraphs [0010]-[0013]. As a probiotic can have can have any number of uses, results, characteristics or mechanisms, no individual use, result, characteristic or mechanism is inherent from referring to a bacterium as "probiotic."

More specifically, not all probiotic microorganisms have the ability to modulate host cyclooxygenase expression profile. See Specification, page 51, lines 30-32. Only specific microorganisms are capable of producing such an effect. See Specification, page 51, line 32 – page 52, line 1. Consequently, the effects of *Bifidobacterium* sp. 420 on epithelial COX gene expression are not inherent from *Bifidobacterium* sp. 420 being termed a "probiotic" bacteria.

Additionally, the Examiner states that "applicant's evidence of surprising results is not commensurate with the scope of the claims. Applicant asserts that the *Bifidobacterium* sp. 420 composition has direct effects on epithelial COX gene expression; however, the claims are directed to any increase in the amount of COX-1 mRNA in any cell of the subject." See Office Action, p. 8-9. Not in acquiescence, but in an effort to expedite prosecution, claim 22 has been amended to recite a microorganism at least increases the amount of a COX-1 mRNA in at least one epithelial cell of the subject.

In view of the above, the claim method provides an unexpected advantage over the method of Collins. Accordingly, claim 22 is patentable over Collins and Van Der Mei. Since claims 23-24 depend from independent claim 22, those claims should be patentable over the combination of Collins and Van Der Mei for at least the reasons described above. Applicants respectfully request reconsideration and the withdrawal of the rejection.

Collins, Van Der Mei, and Zimmer or Chen

The Examiner has rejected claims 22-24 and 28 under 35 U.S.C. § 103(a) as being unpatentable over Collins in view of Van Der Mei, and further in view of U.S. Patent No. 5,501,857 to Zimmer ("Zimmer") or U.S. Patent Publication No. 2001/0014322 to Chen et al. ("Chen"). Claims 23-24 and 28 depend from independent claim 22.

As explained in detail above, Collins and Van Der Mei do not teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-1 mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

Such defects are not remedied by Zimmer or Chen. Zimmer describes an "oral nutritional supplement, i.e., a dietary adjunct, for livestock which includes incompatible live microbial cultures, and vitamin and mineral supplements, each separated from the other via multiple encapsulation." See Abstract of Zimmer. In Example 10 of Zimmer, "[t]he microorganisms are a formulation of commercially available dormant *Bifidobacterium longum*." Zimmer does not teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-1 mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

Chen describes a microbe composition that includes "a symbiotic mixture of three lactic acid producing bacteria consisting of *Bifidobacterium bifidum* 6-1, *Lactobacillus acidophilus* YIT 2004 and *Streptococcus faecalis* YIT 0027." See paragraph [0025] of Chen. Chen does not teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-1 mRNA in at least one cell of the subject, wherein the microorganism is *Bifidobacterium* sp. 420.

None of the above-mentioned references, alone or in combination, teach or suggest teach or suggest a method of treating and/or preventing the side-effects associated with the administration of nonsteroidal anti-inflammatory drugs, which method includes administering to the patient an effective amount of a microorganism, which microorganism at least increases the amount of a COX-1 mRNA in at least one cell of the subject, wherein the microorganism is

Bifidobacterium sp. 420.

Further, none of the cited documents teaches or suggests that a betaine compound (see claim 28) can be used in combination with *Bifidobacterium* in the methods of Collins, let alone that any *Bifidobacterium* strain can act in synergy with betaines in reducing intestinal inflammation. In contrast, the present invention has shown that *Bifidobacterium* sp. 420 can increase the level of COX-1 mRNA in a cell, can reduce intestinal inflammation caused by non-steroidal anti-inflammatory drugs in rats and can act in synergy with betaine for this purpose.

Since claims 23-24 and 28 depend from independent claim 22, those claims should be patentable over the combination of Collins, Van Der Mei and Zimmer or Chen for at least the reasons described above. Applicants respectfully request reconsideration and the withdrawal of this rejection.

CONCLUSION

Applicant believes that the claims are in condition for allowance. Should any fees be required by the present Reply, the Commissioner is hereby authorized to charge Deposit Account 19-4293.

Respectfully submitted,

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